To address this, non-irradiated female BALB/C mice were transplanted with 5-6×107 whole bone marrow (WBM) cells from male BALB/C mice daily for four day on week zero, then again on week eight (4.5×108 cells total/mouse), or an equal volume of diluent (control). On week 24, transplanted mice received 1000 cGy of chest-only radiation or no radiation. On week 32, histochemical and immunohistochemical analyses were performed on recipient's lungs.

Bone marrow chimerism was not significantly different in the irradiated and non-irradiated cohorts at the time of sacrifice (average 45.11 + 6.25% Y chromosome+, all mice). Recipient lungs contained few non-hematopoietic donor marrow-derived cells. These cells were exclusively epithelial (Y+/cytokeratin+), primarily type II pneumocytes (Y+/prosurfactant C+), while no endothelial (Y+/von Willebrand+) or vascular smooth muscle (Y+/alpha-actin+) cells were identified. Irradiated and non-irradiated cohorts had similar quantities of these cells (0.80 + 0.22% vs. 0.51 + 0.08% Y+/cytokeratin+; 0.37 + 0.08% vs. 0.32 + 0.12% Y+/prosurfactant C+, $p > 0.2$). Pulmonary vessel wall thickness-to-blood vessel diameter ratios (PVWT/D) were significantly increased in the non-irradiated cohort compared with controls and these ratios were further increased in the irradiated cohort (141 + 5.75%, 161 + 5.34% of control, $p < 0.05$ comparing all groups).

These data indicated that marrow cell infusion alone results in pulmonary vascular remodeling, and this effect is augmented by radiation injury. These changes are independent of transplanted marrow cell conversion to pulmonary vascular endothelial, smooth muscle cells. These studies suggest that transplanted cells may be lung toxic entities in the setting of clinical BMT.

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MODELS OF STEM CELL TRANSPLANTATION FOR THE REPAIR OF NON-HEMATOPOIETIC TISSUES

Annett, G., Wirthlin, L., Pepper, K., Sondergaard, C., McGee, J., Lindsey, M., Zhou, P., Bauer, G., Nolta, J. University of California, Davis, Sacramento, CA

Human stem cells from adult sources have been shown, in our laboratory and others, to promote the repair of damaged tissues. Different populations of stem cells contribute to the regeneration of muscle, neural tissue, liver, heart, and vasculature, although the mechanisms by which they accomplish this are still not well understood. We and others have shown that stem cells home to hypoxic and/or inflamed areas, and release bioactive factors that can suppress the local immune system, enhance angiogenesis, inhibit fibrosis and apoptosis, and stimulate recruitment, retention, mitosis and differentiation of endogenous tissue-residing stem cells. These trophic effects are distinct from the direct differentiation of stem cells into the tissue to be regenerated. To actually rebuild a non-hematopoietic tissue, the differentiated progeny of embryonic or induced pluripotent stem cells will be required. We have focused on improving rodent models in which to examine human stem cell-mediated disease correction and tissue repair, focusing primarily on liver regeneration and hypoxic tissue models of peripheral vascular disease and cardiac ischemia. Most recently we are studying mesenchymal stem cell–mediated repair of neural damage. We are interested in the mechanisms by which stem cells of different types and origins home preferentially into areas of tissue damage, and we seek to improve the robustness. To track cells into the damaged tissues in vivo, we have labeled them with fluorophore – conjugated iron oxide nanoparticles and have used novel mouse models that facilitate human cell detection. We have also used 19F magnetic resonance imaging for stem cell tracking with multiple unique perfluorocarbon nanobeacons, human/murine centromeric FISH, immunohistochemistry and quantitative PCR. Using these technologies, we have shown that human stem cells migrate from the bloodstream randomly and in moderate numbers throughout all tissues examined in cases of chronic disease or following sublethal irradiation, but that in instances of acute damage, the homing is more vigorous and specific to the site of damage. Pre-culture in hypoxia dramatically alters the phenotype and migratory characteristics of human mesenchymal stem cells. We are applying this knowledge to tissue repair strategies, to allow enhanced numbers of stem cells to migrate to the areas of hypoxic damage, to exert trophic effects that initiate revascularization and cascades of repair.

SUPPORTIVE CARE

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CIDOFOVIR TREATMENT OF BK-VIRUS RELATED HEMORRHAGIC CYSTITIS EARLY AFTER ALLOGENEIC STEM CELL TRANSPLANTATION (HSCT) FOR MALIGNANT DISEASES

Chu, D.T.[1], Gulbis, A.M.[2], Howell, J.E.[2], de Lima, M.[1], Matteo, P.[1], Ciurea, S.[1], Thall, P.F.[1], Champlin, R.E.[1], Andersson, B.S.[1 1] University of Texas M.D. Anderson Cancer Center, Houston, TX; [2] University of Texas M.D. Anderson Cancer Center, Houston, TX

Background: BK virus infection has been associated with late onset hemorrhagic cystitis (HC) after HSCT. Based on data suggesting that cidofovir has activity against BK virus we treated patients with symptomatic HC and high BK virus titers with cidofovir, we now review the outcome of 32 patients undergoing this therapy.

Patients and Methods: The patients studied had undergone allogeneic HSCT for leukemia (28), MDS (1), lymphoma (2), and ovarian cancer (1), and presented with UTI symptoms including (any combination of) hematuria, urgency, and pain, and a high-titer of BK-virus. Patients received treatment with either once weekly (1-5 mg/kg), or divided 3 × weekly/every other day (0.25-0.5 mg/kg/dose). All patients received forced hydration. On the once-weekly schedule 22/23 patients received probenecid and 1/9 in the higher frequency schedule received probenecid. Semi-quantitative BK virus assay was performed prior to and following cidofovir.

Results: A total of 32 patients were treated and the median age was 44 years (range, 23-64), with 17 males and 15 females. Donors were related (n = 13), unrelated (n = 11), haploidentical (n = 2), and unrelated cord blood (CB) (n = 6). The conditioning regimen was myeloablative in 23 pts (72%) and reduced intensity in 9 pts (28%). 24/32 pts (75%) had developed GVHD and were on steroids when diagnosed with BK-UTI. Cidofovir was well tolerated with no subjects developing renal insufficiency. The majority of symptoms were resolved within 10 days from cidofovir initiation but the limited number of subjects precluded a formal comparison between dosing subgroups (Table 1).

The viral load did not change significantly when assessed at a median of 24 days after start of cidofovir (median of $\geq 3.9 \times 10^7$ copies/mL). However, patients who were re-assayed at later time points (median 68 days) had a viral load less than 1% of the initial value (median 4.9×10^5 copies/mL).

We conclude that cidofovir appears promising as treatment for BK-virus related hemorrhagic cystitis. The frequent administration-schedule is relatively easy to administer without the need for probenecid. More data are needed to determine an optimal cidofovir dosing schedule, and optimal time to reassess BK virus load by PCR in allogeneic HSCT patients.

Table 1. Hemorrhagic cystitis symptom response

	Hematuria	Urgency	Cramp/Spasm	Pain	CBI
Pre Cidofovir	28 (88%)	27 (85%)	25 (78%)	30 (94%)	13 (41%)
Post Cidofovir	6 (18%)	9 (28%)	1 (3%)	9 (28%)	1 (3%)

CBI = continuous bladder irrigation.

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A PHASE I DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF PALIFERMIN IN PEDIATRIC SUBJECTS WITH ACUTE LEUKEMIAS UNDERGOING MYELOABLATIVE THERAPY AND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT

Morris, J.[1], Neudorf, S.[2], Moore, T.[3], Shah, A.[4], Graham, M.[5], Aquino, V.[6], Duerst, R.[7], Neidler, M.[8], deChateau, M.[9], Berger, D.[10], Morris, C.[1 1] Loma Linda University Medical Center, Loma Linda, CA; [2] Children's Hospital of Orange County, Orange, CA; [3] Mattel Children's Hospital UCLA, Los Angeles, CA; [4] Children's Hospital, Los Angeles, CA; [5] Arizona Cancer Center, Tucson, AZ; [6] University of Texas Southwestern Medical Center, Dallas, TX; [7] Children's Memorial Medical Center, Chicago, IL; [8] Pediatric Blood and Marrow Consortium; [9] Biovitrum, Stockholm, Sweden; [10] Amgen, Thousand Oaks, CA